Lessons from field synopses
Moving towards an online encyclopaedia

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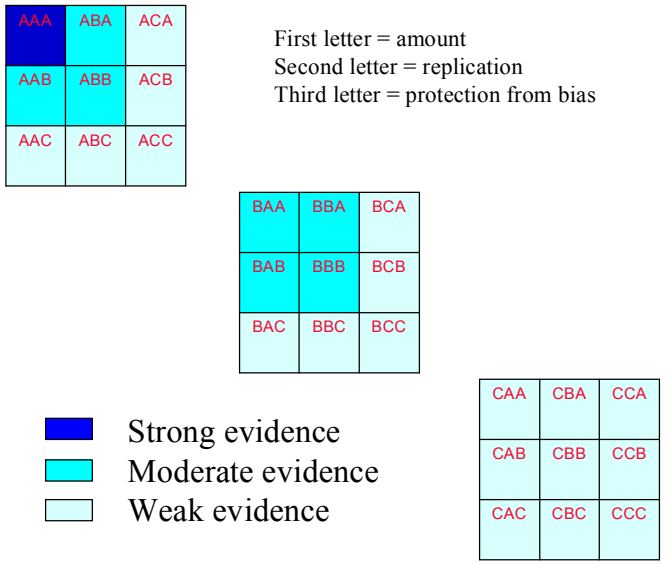
Criteria for assessment of cumulative evidence on genetic associations

1. Epidemiological credibility
   - i. amount of evidence
   - ii. replication
   - iii. protection from bias



if epidemiological credibility is strong:

2. Biological plausibility
3. Clinical and public health importance

Ioannidis et al., 2007

Venice criteria – work in progress

Amount of evidence

- Thresholds may be defined based on sample size, power, or false discovery rate considerations
- The frequency of the genetic variant of interest should be accounted for

Issues with amount of evidence

- Sample size
- Statistical significance
- Alternative approaches to weight the amount of evidence
  - Bayesian methods (FPRP, BFDP)

Replication

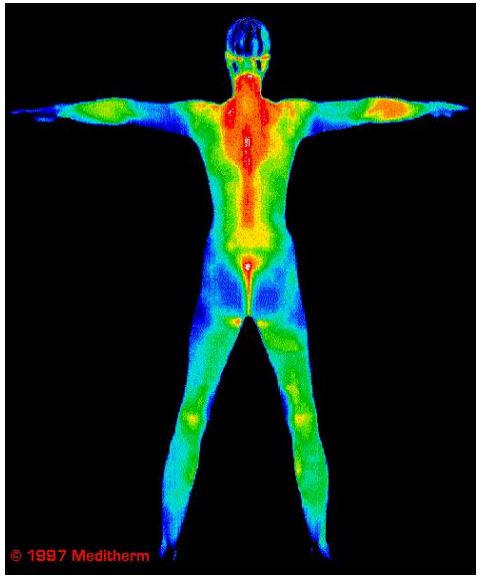
- Statistical considerations
  - I^2, etc.
- Epidemiological considerations
  - comparability of phenotyping, genotyping, and analytical models

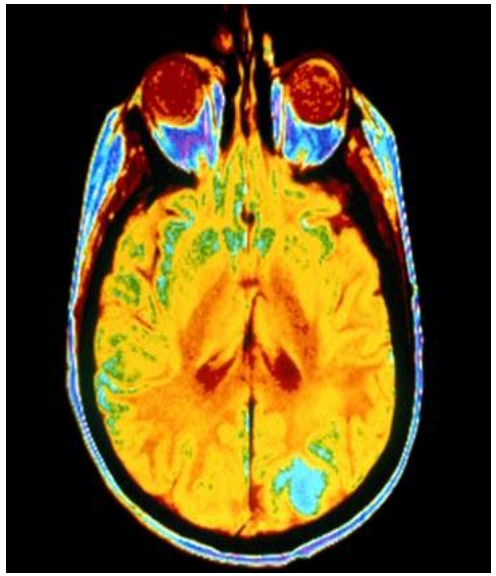
Issues with replication

- Heterogeneity of effect may reflect truth
  - haplotype structure of the population
  - presence vs. magnitude of effect
  - GxE interactions
  - study design
- Heterogeneity of phenotype

Gene-environment interactions

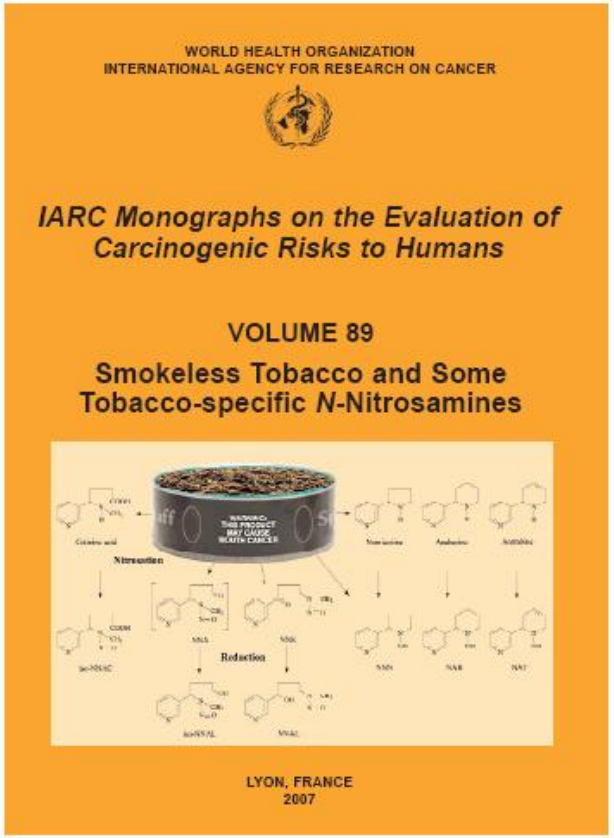
complexity + complexity = complexity





IARC Monographs Classification scheme

Class		Combinations which fit in this class: Human evidence	Animal evidence	Other evidence
1	Established	S	Any	Any
		L	S	+
2A	Probable	L	S	+/-
		I or NA	S	+
2B	Possible	L	< S	Any
		I or NA	S	+/-
		I or NA	L	+
3	Not classifiable	I or NA	L	+/-
		Not elsewhere classified		
		I or NA	-	-
4	Not	-	-	Any



S: sufficient
L: limited
I: inadequate
+: strongly positive
+/-: less than strongly positive
–: strongly negative
NA: not available

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Agents evaluated in IARC Monographs programme, Vol. 1-98

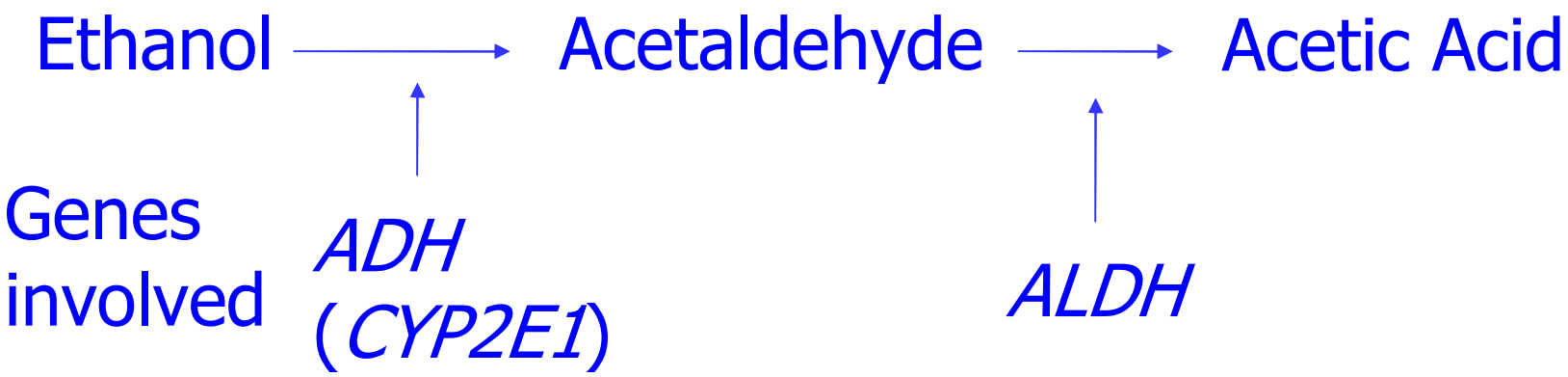
Class	N agents
1 – Established	102
2A – Probable	69
2B – Possible	246
3 – Not classifiable	516
4 – Not carcinogens	1
Total	934

Cancer mortality in France attributable to established risk factors

Risk factor	Men	Women	Both sexes
Tobacco smoking	33.4%	9.6%	23.9%
Alcohol drinking	9.4%	3.0%	6.9%
Infectious agents	3.3%	4.4%	3.7%
Occupational exposures	3.7%	3.4%	2.4%
Overweight and obesity	1.1%	2.3%	1.6%
Lack of physical activity	0.5%	3.2%	1.6%
Exogenous hormones	-	2.2%	0.9%
Ultraviolet radiation	0.6%	0.9%	0.7%
Reproductive factors	-	1.1%	0.4%
Pollutants	0.1%	0.3%	0.2%
Total	45.2%	23.5%	36.7%

NB: attributable risks do not add up!

Alcohol drinking and head/neck cancer



Alcohol is a known carcinogen: the mechanisms are unclear

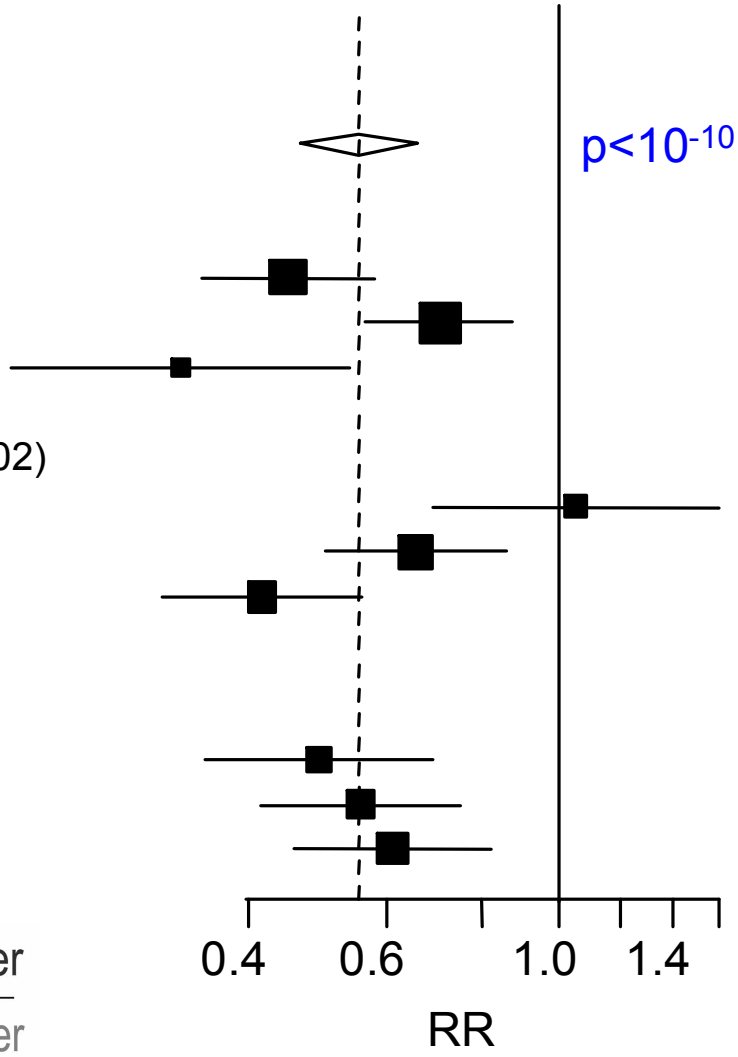
ADH genes govern the rate of elimination of alcohol to acetaldehyde

Individuals may metabolize ethanol up to 100 times faster than others depending on *ADH2* genotype

*ADH2**T (C/T+T/T) vs C/C and head/neck cancer

3 large studies - 3800 cases and 5000 controls
141 Hapmap SNP from 7 *ADH* genes
6 missense variants in 5 *ADH* genes included in the analysis

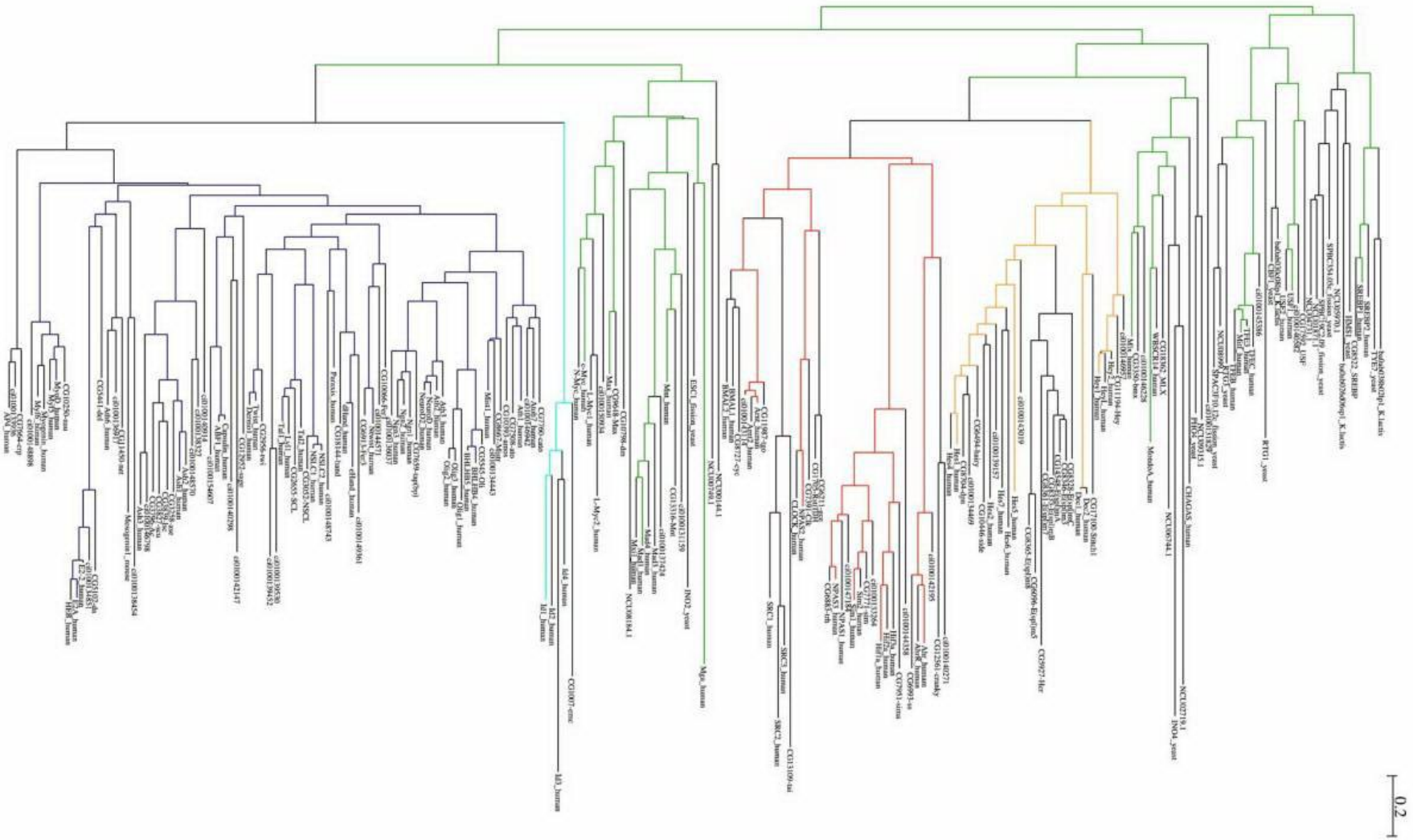
	RR	95%CI
Overall	0.56	0.47-0.66
By site ($p_{heterogeneity}$=0.001)		
Oral/pharynx	0.45	0.35-0.58
Larynx	0.70	0.57-0.88
Esophagus	0.33	0.20-0.54
By drinking intensity (p_{trend}=0.0002)		
Never drinkers	1.05	0.69-1.60
<=Med	0.66	0.50-0.85
>Med	0.42	0.31-0.56
By study ($p_{heterogeneity}$=0.605)		
CE	0.49	0.35-0.69
ARCAGE	0.56	0.42-0.75
LA	0.61	0.46-0.82



Tumour phenotypic variation

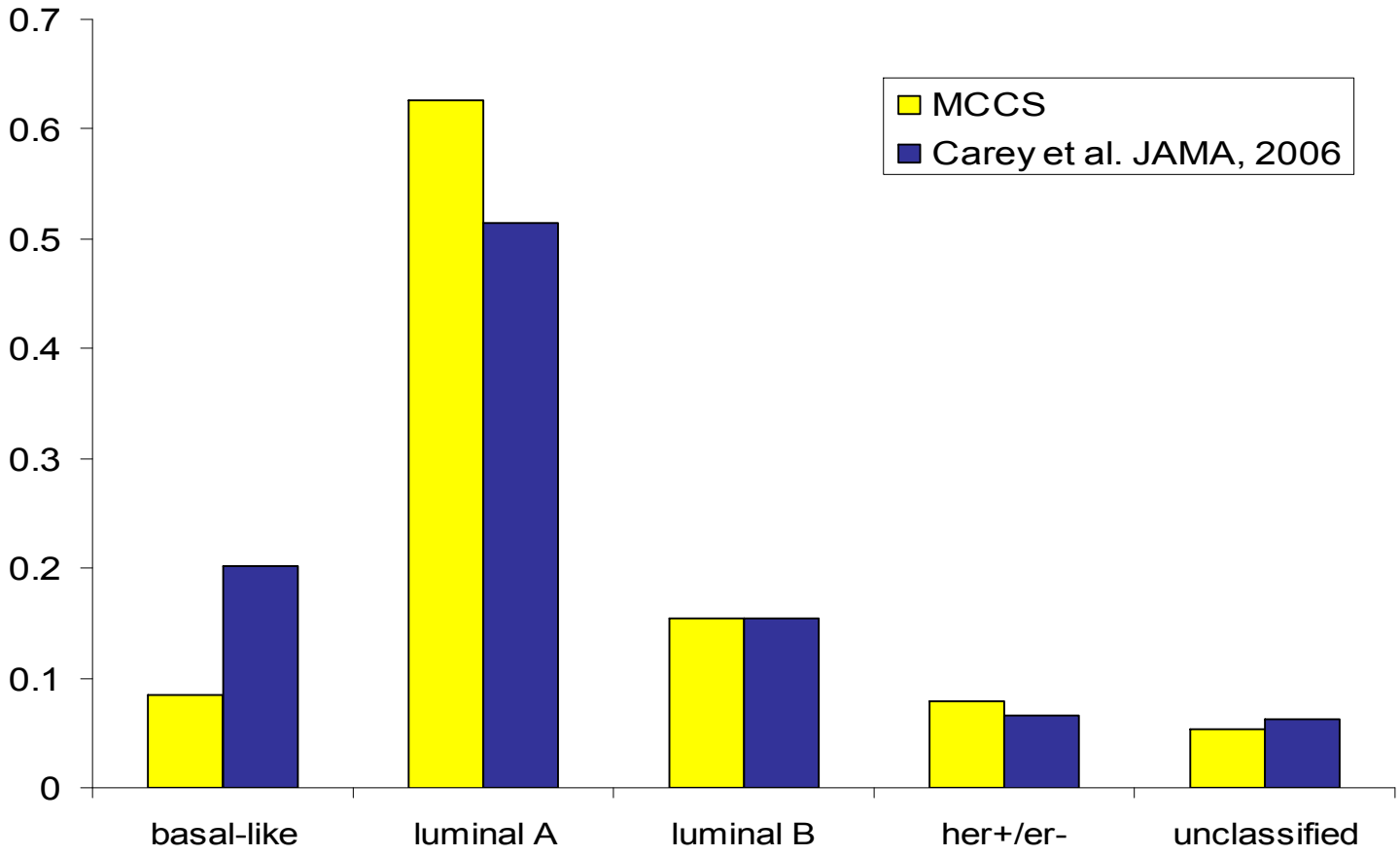
- Historically, cancers in a particular organ are grouped as one disease
- Tumour gene expression analysis identifies subtypes that differ in response to therapy and prognosis
- It is plausible that the subtypes are also aetiologically distinct

Finnish emotional phenotypes



Cluster analysis of tumour gene expression data

Breast cancer subtypes



Protection from bias – grade A

- Phenotype measurement, genotype measurement, confounding (population stratification) and selective reporting in meta-analyses
  - bias appraised to not exceed low levels
- No other demonstrable bias in any other aspect of the design, analysis or accumulation of the evidence

Protection from bias – grade B

- No strong biases apparent
- Information missing on whether major sources of bias have been minimized or accounted

Automated checks for bias

- OR <1.15
- Exclusion of first study
- Exclusion of HWE-violating studies or adjustment for HWE
- Test for small-study effect
- Test for excess of single statistically significant studies

Bias – additional considerations

- Differential genotype or phenotype misclassification
- Evidence for population stratification
- Inappropriate control selection in key studies
- etc.

Table 3 Typical biases and their typical impact on associations depending on the status of the evidence

Biases	Status of the evidence	Likelihood of bias to invalidate an observed association		
		Small OR <1.15	Typical OR 1.15–1.8	Large OR >1.8
Bias in phenotype definition	Not reported what was done	Unknown	Unknown	Unknown
	Unclear phenotype definitions	Possible/High	Possible/High	Possible/High
	Clear widely agreed definitions of phenotypes	Low/None	Low/None	Low/None
	Efforts for retrospective harmonization	Possible/High	Low	Low/None
	Prospective standardization of phenotypes	Low/None	Low/None	Low/None
Bias in genotyping	Not reported what was done	Unknown	Unknown	Unknown
	No quality control checks	Possible/High	Low	Low
	Appropriate quality control checks	Low	Low	Low/None
Population stratification	Not reported what was done	Unknown	Unknown	Unknown
	Nothing done[a]	Possible/High	Possible/High	Possible/High
	Same descent group[b]	Possible/High	Low	Low/None
	Adjustment for reported descent	Possible/High	Low	Low/None
	Family-based design	Low/None	Low/None	Low/None
	Genomic control, PCA or similar method	Low/None	Low/None	Low/None
Selective reporting biases	Meta-analysis of published data	Possible/High	Possible	Possible
	Retrospective efforts to include unpublished data	Possible/High	Possible	Possible
	Meta-analysis within consortium	Low/None	Low/None	Low/None

Beyond epidemiological credibility

- "Future empirical research and consensus development are needed to develop an integrated model for combining epidemiological and biological data..."

- Biological plausibility
- Clinical and public health importance

Biological plausibility – lines of evidence

- Function of the variant or associated gene, which may make it a plausible candidate for association with the phenotype under study
- Type of amino acid change, location, evolutionary conservation
- Transgenic animal models, gene expression studies
- Ad-hoc experiments vs. routinely annotated information

Criteria for biological plausibility

- Strength and consistency of biological effects
- Amount of data
- Number of different lines of corroborating evidence
- Relevance of the biological system to the phenotype
- Extent of replication
- Protection from bias

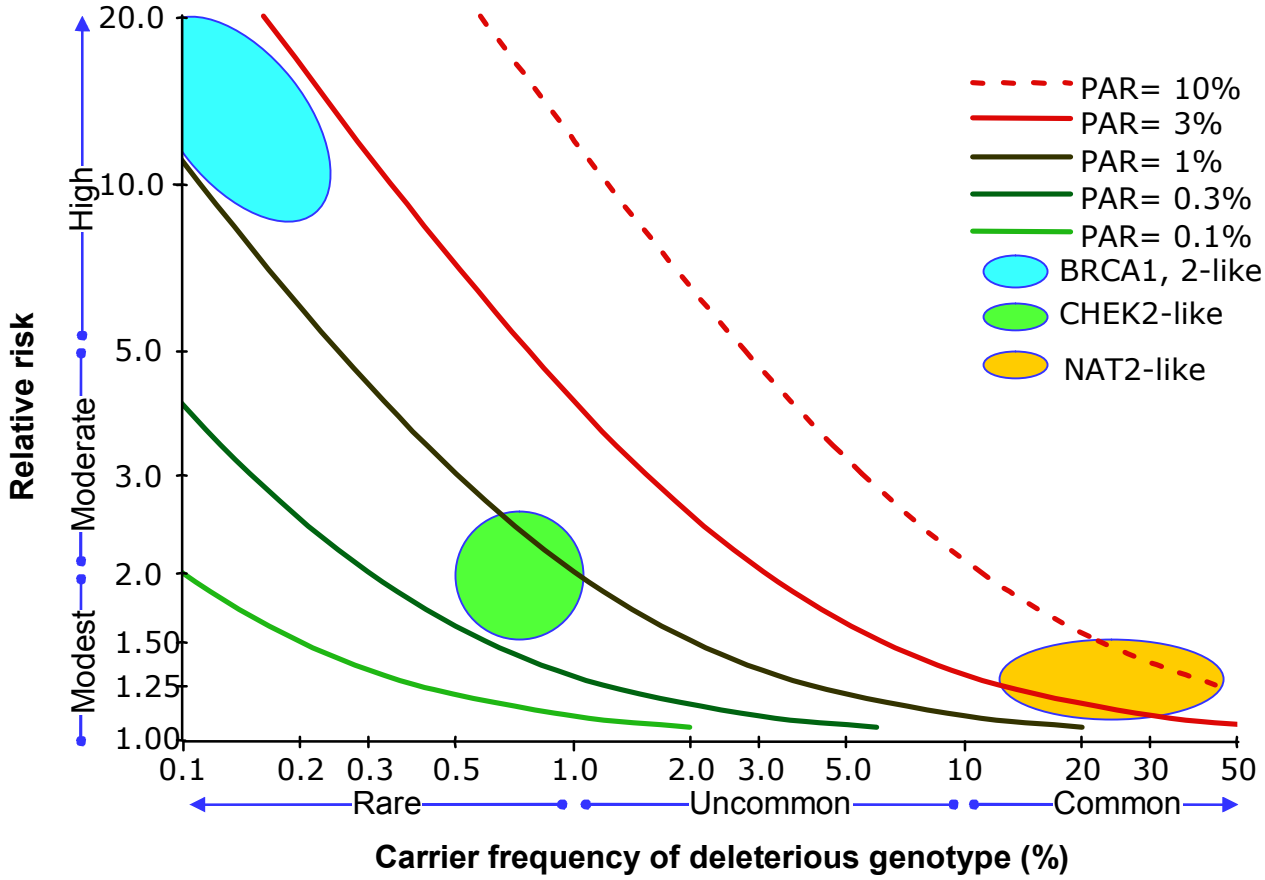
Biological plausibility

- Complex and variable information; difficult to generalize on the importance of each piece of information
- Examples of misleading use of additional evidence to support or refute an association
- Non-epidemiological evidence alone is unlikely to be sufficient to make an association highly credible

Criteria for clinical and public health importance

- Attributable risk
  - effect size
  - frequency of genetic variant in population
  - AR for multiple variants
- Type of phenotype
  - biological, endophenoype, hard clinical outcome
- Disease burden
  - incidence, severity, and mortality
- Interaction with identified modifiable environmental exposures
- Potential to prevent disease through intervention
  - Mendelian randomization insights

Relative risk, carrier frequency, and population attributable risk



Incorporating the three dimensions

- No detailed guidelines for rating biological plausibility and clinical/public health relevance
  - associations with weakly credible epidemiologic evidence and very strong biological plausibility
  - associations with strong epidemiologic credibility and very limited biological data

Moving towards an online encyclopaedia

- Performing the field synopses
  - selection of variants and phenotypes
  - entry criteria (e.g., number of studies)
  - inclusion of GWA results
  - who grades the evidence?
- Updates of field synopses
- Evolution of Venice criteria

A plea for a conservative approach in grading the evidence

- An 'A' rating should be definite
- All other ratings should be seen as preliminary and subject to change as evidence evolves
- A 'B' rating for an association with strong prior may help to identify areas for future research

Jean Huber - Le repas des philosophes (1772-73)